# REMARKS

### Formal Matters

A substitute specification, revised sequence listing and formal drawings are provided in order to correct various errors of form. Responsive to the Examiner's remark concerning the priority information, the paragraph at page 1, line 12 has been appropriately revised.

In amended Figures 1A-1E, Figures 2A-2B, Figures 3A-3D, Figure 4, Figure 5, Figures 6A-6F, Figure 7A-7B, Figure 8A-8D, Figure 9, Figure 10A-10D and Figure 11A-B, extraneous text was removed from the Figures.

Claims 29-54 remain in this application. No claim has been canceled. Claims 29, 39 and 49 are amended. No new matter is added by the amendments.

Support for the amendments to claims 29, 39, 49 is found at least at page 49, lines 33-36.

In view of the Examiner's earlier 6-way restriction requirement in parent application USSN 09/292,505, now U.S.P. 6,348,575, applicant retains the right to present previously withdrawn and cancelled claims in a divisional application.

### The Rejection under 35 U.S.C. § 101

Claims 29-34, 37, 39-44, 47, 49-50 and 53 are rejected under 35 U.S.C. § 101 allegedly for being directed to non-statutory subject matter.

In response, Applicants amendment renders the rejection moot.

# The Rejection under 35 U.S.C. § 102(e)

Claims 29-35, 37-45, 47-51, and 53-54 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,309,879. Specifically, the Examiner has alleged that the above claims are drawn to antibodies which bind to polypeptides that are at least 91%, 92%, 93%, 95% or 100% identical to SEQ ID NO:2. The Examiner further alleges that the '879 patent not only teaches a polypeptide sequence that is 99.6% identical to SEQ ID NO:2, but also antibodies binding to such polypeptide sequence.

Appl. No. 09/990,046 Amend. dated March 21, 2005 Response to Office Action mailed on: December 20, 2004

In response, Applicants respectfully submit that the 6,309,879 patent was the losing party to Applicants' related application USSN 09/060,939, having the same inventors and filing date as the parent application (USSN 09/292,505, U.S.P. 6,348,575) of the pending application. The U.S.P.T.O. has already determined in a prior action that Applicants are the actual inventors of the subject matter claimed in the '879 patent. A copy of the final decision from Interference 105,081 awarding all of claims 1-13 of '879 patent to Applicant's 09/060,939 application appears in the Appendix.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 29-35, 37-45, 47-51, and 53-54 under 35 U.S.C. § 102(e)

# The Rejection Under 35 U.S.C. § 103(a) (cited references)

Claims 36, 46, and 52 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over the '879 patent as applied to claims 29-35, 37-45, 47-51, and 53-54 above, and further in view of Berkower.

In response, Applicants response above under the 102 reference has eliminated the relevance of the '879 patent to the pending claims. Berkower does not teach, disclose or infer antibodies that bind SEQ ID NO:2.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 36, 46 and 52 under 35 U.S.C. § 103(a).

Appl. No. 09/990,046

Amend. dated March 21, 2005

Response to Office Action mailed on: December 20, 2004

**SUMMARY** 

Patent Docket P1405R1C1

Claims 29-54 are pending in the application. Claims 29, 39 and 49 have been amended

without prejudice to later prosecution.

If in the opinion of the Examiner, a telephone conference would expedite the

prosecution of the subject application, the Examiner is strongly encouraged to call the

undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter. In the unlikely event that

this document is separated from the transmittal letter or if fees are required, applicants petition

the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or

credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

GENENTECH, INC.

Date: March 21, 2005

Craig G.)Svoboda

Reg. No. 39,044

Telephone No. (650) 225-1489

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# Appendix

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T-597 P.002/004 F-011

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 13

Filed by:

Trial Section Merits Panel Box Interference 20231

Filed 4 April 2003

Washington, D.C. Tel: 703-308-9797 Fax: 703-305-0942

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

DAVID A. BUMCROT,

Junior Party (Patent No. 6,309,879),

FREDERIC DE SAUVAGE and DAVID A. CARPENTER, PAT, & T.M. OFFICE BOARD OF PATENT APPEALS AND INTERFERENCES

Senior Party (Application No. 09/060,939).

Patent Interference 105,081 (NAGUMO)

Before SCHAFER, LANE, and NAGUMO, Administrative Patent Judges. NAGUMO, Administrative Patent Judge.

> JUDGMENT (Pursuant to 37 CFR § 1.662(a))

## Introduction

On April 2, 2003, junior party Bumcroft filed Paper 12, in which it conceded priority as to Count 1, the sole count in this interference, and acknowledged that the communication would be treated as a request for adverse judgment.

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T-587 P.009/004 F-011

Paper No. 13

Interference 105,081 Bumcrot v. De Sauvage

### order

On consideration of the forgoing, it is:

ORDERED that judgment on priority as to Count 1 is awarded against junior party Bumcrot,

FURTHER ORDERED that Bumorot is not entitled to a patent containing claims 1-13 of Bumorot's 6,309,879 patent, which correspond to Count 1;

FURTHER ORDERED that copies of this decision be given appropriate paper numbers and be entered in the administrative record of Bumcrot's 6,309,879 patent and De Sauvage's 09/060,939 application.

RICHARD E. SCHAFER

Administrative fatent Juge

SALLY GAZDNER LANE

Administrative Patent Judge

MARK NAGUMO

Administrative/Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

INTERFERENCE TRIAL SECTION

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T-597 P.004/004 F-011

Paper No. 13

Interference 105,081 Bumcrot v. De Sauvage

cc (via Facsimile and first class mail):

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Fax: 650-324-6653

- 3 -

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Caller

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GCCGCGAAAC ACGTCGACCG GGTCCTCCGG GACGGACTCT TGCGAAGGGT CGTCTAGGTA CGGAAGAGGA GGTGGTGGGA CCTACTGTAG GACGTACGCA 1301 CGGCGCTTTG TGCAGCTGGC CCAGGAGGCC CTGCCTGAGA ACGCTTCCCA GCAGATCCAT GCCTTCTCCT CCACCACCCT GGATGACATC CTGCATGCGT LHA F. ۲ A н S S z u ם A E α 0 357

1401 TOTOTGANGT CAGTGOTGCO CGTGTGGTG GAGGOTATOT GCTCATGCTG GCCTATGCOT GTGTGACCAT GCTGCGGTGG GACTGCGCCC AGTCCCAGGG CTGACGCGG TCAGGGTCCC დ დ AGAGACTICA GICACGACG GCACACCACC CICCGATAGA CGAGIACGAC CGGAIACGGA CACACTGGIA CGACGCCACC ٠, V T A Y A C Σ ٦ G Y L R V V G A A ഗ 397

GAACGECECE ATGACGACEA CEGGGACEGE CACEGGAGTE EGGAACECEGA GACAEGGGAE GAGEGGTAGT GGAAGTTACG AEGGTGATGG 1501 TICCGIGGGC CTIGCCGGGG TACTGCTGGT GGCCCTGGCG GTGGCCTTAGGCT CTGTGCCCTG CTCGGCATCA CCTTCAATGC TGCCACTACC H e A Z н ७ CA ഗ S A > 'A L A L L L A G AAGGCACCCG ഗ s S 1501 CAGGIGCTGC CITTCTTGGC TCTGGGAATC GGCGTGGATG ACGTATTCCT GCTGGCGCAT GCCTTCACAG AGGCTCTGCC TGGCACCCCT CTCCAGGAGC GICCACGACG GAAGAACCG AGACCCITAG CCGCACCIAC IGCATAAGGA CGACCGCGTA CGGAAGTGIC ICCGAGACGG ACCGIGGGGA GAGGICCICG 0 A L P A F T E LAH > ₽ G V D r G H A L >

1701 GCATGGGCGA GTGTCTGCAG CGCACGGGCA CCAGTGTCGT ACTCACATCC ATCAACAACA TGGCCGCCTT CCTCATGGCT GCCCTCGTTC CCATCCCTGC CETACCEGET CACAGACGIC GCGIGCCCGI GGICACAGCA TGAGIGIAGG TAGIIGITGI ACCGGCGGAA GGAGIACCGA CGGGAGCAAG GGIAGGGACA L M N N H t E O Σ

TGCTCAGGTG ATTCAGATCC TGCCCCAGGA GCTGGGGGGAC GGGACAGTAC GGATGCCGCC TCACCAACCG ACGTGGAAAC ATCGGCACTA CGAACAGAAG GGTCGGTAGG AGTCGGACCT TGCACCTTTG TAGCCGTGAT GCTTGTCTTC CCAGCCATCC TCAGCCTGGA Н æ p. ĹĽ > ,ــ Σ > ۲ TTCTCCCTAC AGGCGGCCAT AGTGGTTGGC > > CGACGCTCGG AAGAGGGATG TCCGCCGGTA 1801 GCTGCGAGCC

CCCTGTCATG > TAAGTCTAGG ACGGGGTCCT CGACCCCTG ග Ø p. о н ACACGAGACG ACGAAGAGGT CAGGGACGAG ACGAGTCCAC A Q V 1901 CGCCACTGCC AGCGCCTTGA TGTGCTCTGC TGCTTCTCCA GTCCCTGCTC U p, ſL, ר. > GCGGTGACGG TCGCGGAACT ж :1 :О U 'n. 557

CCAGTGGTAG GACGGAGGGG TTCGGGTGGA GCCAGCATGT GGTCACCATC CTGCCTCCCC AAGCCCACCT Ω, ם Н E > ATGGGTGACA CTTCGGTCGT CGGTCGTACA > H α ACTGCCACAG TTCAAGCCTT TACCCACTGT GAAGCCAGCA A S ш U H € TGACGGTGTC AAGTTCGGAA Ø > T A 2001 CAGTGGGCAT TGCCCACCTC GTCACCCGTA ACGGGTGGAG :r: 591

GGCCAGGAGG AGGAGACAAG GCAGAAGGCA CGTCTTCCGT CCTGGAAGAT CCGGTCCTCC TCCTCTGTTC GGACCTTCTA GETGCCCCCA CCTTCTGACC CACTGGGCTC TGAGCTCTTC AGCCCTGGAG GGTCCACACG

E ជោ ū တ ပ ü Ω GGAAGACTGG GTGACCCGAG ACTCGAGAAG TCGGGACCTC CCAGGTGTGC € ഗ ပ S **,**\_1 ш ഗ ٠, Ω CCACGGGGGT > 624

CGGTAGCACG GCCCCGTTGC TGCTCCAGIC ACATGCCAAG GCCATCGTGC AIV TGTACGGTTC × CGGACGTTCA GGGACGGGAC ACGGGCGACC TTAGAACGGG TAAAGCGGGC GATAGTCAAA CGGGGCAACG ACGAGGTCAG 2201 GCCTGCAAGT CCCTGCCCTG TGCCCGCTGG AATCTTGCCC ATTTCGCCCG CTATCAGTTT С Гч >-A ĹĻ Z L P 3 æ O. 657

GACGGATGTG GTGCCTCGGG GCACCAAGGA CACGGAGCCC CGTGGTTCCT × O. CTGCCTACAC > 0 H CTGGGCCTGA GCCTCTACGG AGCCACCTTG GTGCAAGACG GCCTGGCCCT TOGGTGGAAC CACGTTCTGC CGGACCGGGA LAL 0 0 > Ŧ æ ACCACGAGAA ACCACGAGAA GACCCGGACT CGGAGATGCC ... ... 1 0 1 2301 TGGTGCTCTT TGGTGCTCTT ٠., رد دن ر. د. 691

AAACTGATGC GGGTAAGGGT TGCGCGGGAG TTTGACTACG CCCATTCCCA ACGCGCCCTC æ × γ Q 2401 GCATGCCTTC CTGAGCGCCC AGCTCAGGTA CTTCTCCCTG TACGAGGTGG CCCTGGTGAC CCAGGGTGGC CGTACGGAAG GACTCGCGGG TCGAGTCCAT GAAGAGGGAC ATGCTCCACC GGGACCACTG GGTCCCACCG ს ს c. E < A κ >-A S :[

AACTGGCTAC TTGACCGATG GATAATGGCG CTATTACCGC **∀** TITGAICTEC ACCAGCECTI CAGITCCCIC AAGGUGGIGC IGCCCCCACC GGCCACCCAG GCACCCCGCA CCIGGCIGCA AAACTAGACG TGGTCGCGAA GTCAAGGGAG TTCCGCCACG ACGGGGGTGG CCGGTGGGTC CGTGGGGCGT GGACCGACGT æ A P O (-Æ a a D, ХАХ ٦. ഗ ഗ 14 14 C) 2501

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FIG. 1C

ГЛ 2701 GCTCATCCAG ACTGGAGAGG CCCAGGAGCC TCTGGATTTC AGCCAGCTGA CCACAAGGAA GCTGGTGGAC AGAGAGGGAC TGATTCCACC ω CGAGTAGGTC TGACCTCTGC GGGTCCTCGG AGACCTAAAG TCGGTCGACT GGTGTTCCTT CGACCACCTG ٦ Ω د. ω

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TACATEGEGC TGACCETETE GETGAGCAGT GACCCCCTGG GTCTGGCAGC CTCACAGGCC AACTTCTACC CCCCACCTCC TGAATGGCTG CACGACAAAT × Он 3 GAGTGTCCGG TTGAAGATGG GGGGTGGAGG Ω, ρι D, >-(L, д О ഗ CCACTCGTCA, CTGGGGGACC CAGACCGTCG L A D P L G ഗ **;**> ATGTACCCCG ACTGGCACAC ×. 2801 857

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CTGGGGTGCA CGCCTACCCC AGCGGCTCCC CCTTCCTCTT CTGGGAACAG GCGGATGGGG TCGCCGAGGG GGAAGGAGAA GACCCTTGTC 0 ᇤ (L, ഗ ტ മ × × TAGCTCCCCC GGGCCCGTCG TACGCGTCTC CGGCCGGTCC GACCCCACGT TGTGGAGGCC ATCGAGGGGG CCCGGCCAGC ATGCGCAGAG GCCGGCCAGG 4 0 O A U A æ ഗ ACACCTCCGG ដោ 924 3001

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3501 CGGCGCTGAC ACTGCTCACG CTCCTGGGCC TCCTCCATGG ACTCGTGCTG CTGCCTGTGC TGCTGTCCAT CCTGGGCCCG CCGCCAGAGG TGATACAGAT GCCGCGACTG TCACGAGTGC GAGGACCCCGG AGGAGGTACC TGAGCACGAC GACGGACACG ACGACAGGTA GGACCCGGGC GGCGGTCTCC ACTATGTCTA ပ ij 7 V G X G L' L ι. :>

3501 GTACAAGGAA AGCCCAGAGA TCCTGAGTCC ACCAGCTCCA CAGGGAGGCG GGCTTAGGTG GGGGGCATCC TCCTCCCTGC CCCAGAGCTT TGCCAGAGTG TOGGGTCTCT AGGACTCAGG TGGTCGAGGT GTCCCTCCGC CCGAATCCAC CCCCGTAGG AGGAGGGACG GGGTCTCGAA ACGGTCTCAC ഗ <u>ი</u> d d a CATGTTCCTT

3701 ACTACCTCCA TGACCGTGGC CATCCACCCA CCCCCCTGC CTGGTGCCTA CATCCATCCA GCCCCTGATG AGCCCCTTG GTCCCTGGT GCCACTAGCT TGATGGAGGT ACTGGCACCG GTAGGTGGGT GGGGGGGACG GACCACGGAT GTAGGTAGGT CGGGGACTAC TCGGGGGAAC CAGGGGACGA CGGTGATCGA P P L >

3801 CTGGCAACCT CAGTTCCAGG GGACCAGGTC CAGCCACTGG GTGAAAGAGC AGCTGAAGCA CAGAGACCAT GTGTGGGGCG TGTGGGGTCA CTGGGAAGCA

GACCGTTGGA GTCAAGGTCC CCTGGTCCAG GTCGGTGACC CACTTTCTCG TCGACTTCGT GTCTCTGGTA CACACCCCGC ACACCCCAGT GACCCTTCGT

3901 CTGGGTCTGG TGTTAGACGC AGGACGCCCTGGAGGGC CCTGCTGCTG CTGCATCCCC TCTCCCGACC CAGCTGTCAT GGGCCTCCCT GATATCGAAT A T G 0 9 d 9 æ ഗ

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	905531	80 GTATCTGGGCCTG	** * ***	* ****	* ** ** *	** ***
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	905531	130 TGTGCACTTTCCT **** ****	*** ** ***	* * ** *	****	****
	hpatched 31	CCTGCACATTCCT	CGTGTGCGCT 3130	GTCTTCCTTC 3140	TGAACCCCTG 3150	GACGGCC
	.905531	180 GGCCTNATAGTGC ** *** ***	*****	* ****	** ** ** *	* ** **
	hpatched	GGGATCATTGTGA	TGGTCCTGGC 3180	GCTGATGACO 3190	GGTCGAGCTGT 3200	'TCGGCAT
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        GCACTTTCCTCNTCTGTGCTCT
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        GCGCTGTCTTCCTTCTGAACCC
hpatched
               3140
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GRRRATGGLRRAAAPDRD. PGRPAG PODRGGGGGGGIGA

GGRR

ш ⋖

AGNA

⋖

(SEQ ID NO:4) PTCH (SEQ ID NO:2) PTCH2

PSYCDAAFALEOISKGKATGRKAPLWLRAKFORLLFKLGCYIOKNCGK PSYTPP.-ARTAAPOILAGSLKAPLWLRAYFOGLLFSLGCGIORHCGK Œ a. PTCH2

101 FILVVGILL HEGAFAVGIKAANLETNVEELWVEVGGRVSREINYTROKIGEE 58 VIFLGLLAFGALALGLAMA! IETNLEOLWVEVGSRVSOELHYTKEKILGEE

AMFNPOLMIOTPKEEGANVLTTEALLOHLOSALOASRVHVYMYNROWKLE AAYTSOMLIOTAROEGENILTPEALGLHLOAALTASKVOVSLYGKSWOLN PTCH2

[O O HLCYKSGELITETGYMDOIIEYLYPCLIIITPLDCFWEGAKLOSGTAYLL KICYKSGVPLIENGMIEWMIEKLFPCVILTPLDCFWEGAKLOGGSAYLP 158 PTCH2

 $\triangleleft$ KPPLRWTNFDPLEFLEELKKINYOVDSWEEMUNKAEVGHGYMDRPCLNP, RPDIOWTNLDPEOLLEELGPFA.SLEGFRELLDKAOVGOAYVGRPCLHPI 251 PTCH2

DPDCPATAPNKNSTKPLDMALVLNGGCHGLSRKYMHWQEELIVGGTVKNS DLHCPPSAPNHHSRQAPNVAHELSGGCHGFSHKFMHWQEELLLGGMARDP 301

TIGKILVSAHALOTMFOLMTPKOMYEHFKGYEYVSH-TNWNEDKAAAILEAW OGELL RAEALOSTELLMSPROLYEHFRG·DYOTHOLGWSEEQASTVLOAW 351 307

TYVVEVVHOSVAONSTOKVLSFTTTTLDDILKSFSDV3V RVASGYLLM RFYJOLAOEALPENASOOIHAESSTTLDDILHAFSEVSAARVVGGYLLM 0 0 PTCH2

< < FNAF SH TM3 61 A 6 V L L V A L S V A A G L 6 L 0 S L 1 G T 1 6 L A 6 V L L V A L A V A S G L 6 L C A L L G L Q G A V Q တ တ LAYACLEMERWDGSK LAYACVTMERWDGAO 450 406 PTCH2

T G Q N K R I P F E D R T G E C L K R T G A S V A A A L P G . . T P L Q E R M G E C L Q R T G T S V V AHAFSET AHAFTEP 0 V F L L / TM4

TOVLPFLALGIGNDD

TOVLPFLALGIGNDD 456 PTCH2

TM6 SLOAAVVVVFNFAWVLLIFPATLSMD SLOAATVVGCTEVAVMLVERALLSLD A A TMS LTSINNVTAFFMAAL VP. P.ALR 550 PTCH2 PTCH

တေ > d  $\mathbf{r}$ SS >-o⊥ a. RLD I FCCF TSPCVSRVIOVEPOAYTOTHONTRYSPPI RLDVLCCFSSPCSAOVIOILPOELGOGT..... REDRA > R R R 554 PTCH PTCH2

T L S C HTHVYYTTTAEPRSEISVQPVTVTQD SSQHVVTILPPQAHLVPPP-...SD S T V O L R T E Y D P H A T V O A F T H C E A S ITMQS ..LTA O ш A H H H 650 PTCH2 PTCH

പ ഗ LEPPOTKWTLSSFAEKHYAPFLLK KSLPCARWNLAHFARYOFAPLLLO L H - - - O K A A O L S S F <u>о</u>. ш ESTSSTROLLSOFSI SPGGSTROLLGOEE ა പ പ O ш 700 PTCH2

× 0 <u>ட</u> ப FIAAOF TM7 Karvvvi i fich egeegvs<u>tyg</u>ttrivadelaltovvpretikenal hara ivlvvetgaleegvgaltivadelaltovvpregikenal 748

K M W L H FYNMY IVTOKA - DYPNIOHLLYDLHRSFSNVKYVMLEENKOLPI LYEVALVTOGGFDYAHSORALFDLHORFSSLKAVLPPPATOAPI SS ս. ս.

FIG. 3B

YFROWLOGLODAFDSDWETGKIMPNNYKNGSDOGVLAYKLLVOTGSRDKP YYRNWLOGIOAAFDODWASGRITRHSYRNGSEDGALAYKLLIOTGDAOEP 784

DISOLTKORLVDADGIINPSAFYIYLTAWVSNDPVAYAASOANIRPHRPDFSOLTTRKLVDREGLIPPELFYMGLTVWVSSDPLGLAASOANFYPPPP PTCH2

EWVHOKADYMPETRILRIPAAEPIEYAOFPFYUNGLRDTSDFVIEWUHDKYD TTGENLRIPPAOPLEFAOFPFLLRGLOKTADFV 884 PTCH2

CAVE CALL I GSNYTSLGLSSYPNGYPFLFWEOY I GLRHWULLFTSVYURCTFLY. A CAEAGOAGVHAYPSGSPFLFWEOYLGLRRCFLLAVCILUVGTFLY. 933 664 PTCH2 PTCH

TM8

GVEF GVEF TM9

LUNPWTAG 170 MVLALMTVELFGMMGL1G1KLSAVPVV1E 1/ASVG1 1047

m I TM11 TVHVALAFLTA IGDKNRRAVLALEHMFAPVLDGAVSTLLGVLMLAGSI TVHVALGFLTTOGSRNLRAAHALEHTFAPVITDGAIISTLLGVLMLAGSI 1033

മഗ **\_** u G L N R L TM12 FAVER ET LEGVENGE VELPVELS FREPPPEVSPANI FAALTVETEEGELHGE VELPVELS FEGPPPEVIOMY 1083

യ പ 000 ш ∢ 1197

FIG. 3C

PTCH 1247 AGG|PA|HQVIVEATENPVFAHSTVVHPESRHHPPSNPRQQPHLDSGSLPPG PTCH2 1182 PWS|PA|ATSSGNLSSRGPGPATG

PTCH 1297 ROGOOPRRDPPREGLWPPLYRPRRDAFEISTEGHSGPSNRARWGPRGARS

PTCH 1347 HNPRNPASTAMGSSVPGYCOPITTVTASASVTVAVHPPPVPGPGRNPRGG

PTCH 1397 LCPGYPETDHGLFEDPHVPFHVRCERRDSKVEVIELQDVECEERPRGSSS

PTCH 1447 N

FIG. 3D

Upper 💍

**4**.4 Kb

Lower

↓ B Actin

FIG. 4

t ent

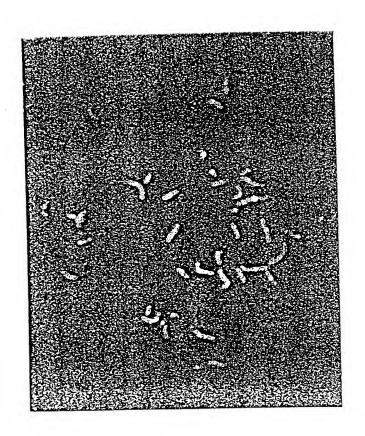
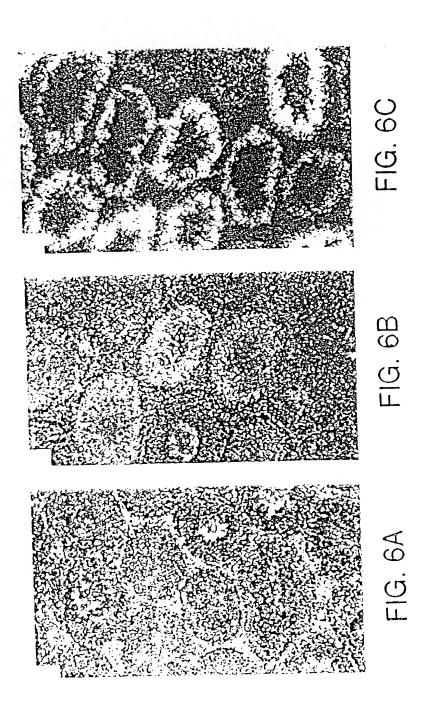
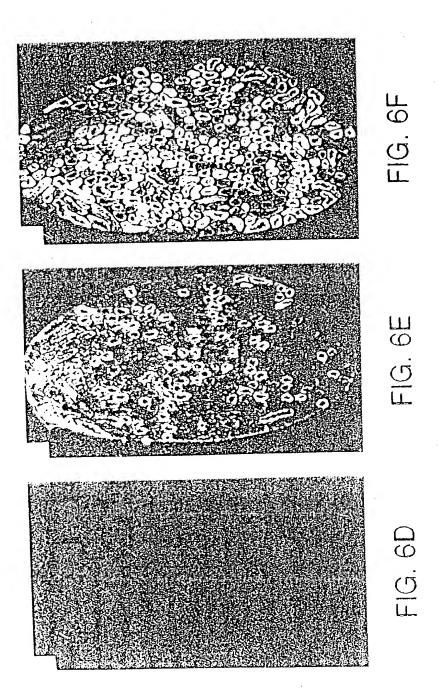
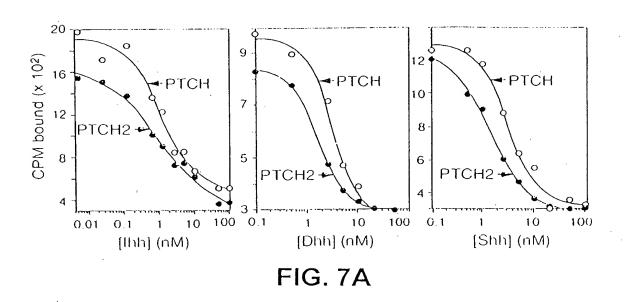


FIG. 5







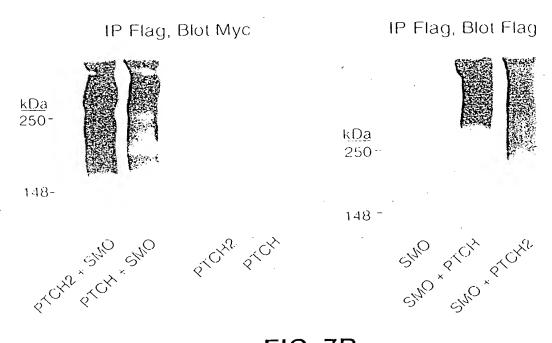


FIG. 7B

hPtch-2	10 MTRSPPLRELPPSY * ** *****	20 TPPARTAAPQ	30 ILAGSLKAPL *****	40 WLRAYFQGLL ******	50 FSLGCG ****
mPatched2	MVRPLSLGELPPSY	TPPARSSAPH 20	ILAGSLQAPL 30	WLRAYFQGLL 40	FSLGCR 50
hPtch-2	60 IQRHCGKVLFLGLI **.****** IQKHCGKVLFLGLV	****	.*.***.**	****	****
h <i>Ptch-</i> 2 mPatched2	110 KEKLGEEAAYTSQN ******** KEKLGEEAAYTSQN 110	****	* . * * * * * * . *	*****	****
h <i>Ptch-</i> 2 mPatched2	160 GKSWDLNKICYKS ************ GKSWDLNKICYKS	********** GVPLIENGMIE	ERMIEKLFPC	*********** VILTPLDCFWE	****
h <i>Ptch-</i> 2	160 210 GSAYLPGRPDIQW ******	170 220 TNLDPEQLLEI	230 ELGPFASLEG	190 240 FRELLDKAQVC	250 GQAYVGR
mPatched2	GSAYLPGRPDIQW 210	TNLDPQQLLE	ELGPFASLEG 230	FRELLDKAQVO 240	GQAYVGR 250
h <i>Ptch-</i> 2 mPatched2	260 PCLHPDDLHCPPS ***.*** ***** PCLDPDDPHCPPS 260	***.***** SAPNRHSRQAP	***.***** NVAQELSGGC	***	ZEELLLG
h <i>Ptch-</i> 2 mPatched2	310 GMARDPQGELLRA * *** ** **** GTARDLQGQLLRA 310	*****	*****	*****	* * * * * *

FIG. 8A

h <i>Ptch-</i> 2	360 VLQAWQRRFVQLA( ************ VLQAWQRRFVQLA(	****	****	*** ***	****
mPatched2	360	370	380	390	400
h <i>Ptch-</i> 2 mPatched2	410 GYLLMLAYACVTM ******** GYLLMLAYACVTM	*********. LRWDCAQSQG <i>P</i>	********* VGLAGVLLVA	****	***
h <i>Ptch-</i> 2	410 460 FNAATTQVLPFLA	420 470 LGIGVDDVFLI	430 480 LAHAFTEALPO	490 GTPLQERMGEO	500 CLQRTGT
mPatched2	************* FNAATTQVLPFLA 460	*******.*** LGIGVDDIFLI 470	LAHAFTKAPPI 480	OTPLPERMGEO	CLRSTGT 500
h <i>Ptch-</i> 2	510 SVVLTSINNMAAF ** ***.*** **	****	****	**** * ***	****
mPatched2	SVALTSVNNMVAF	FMAALVPIPA 520	LRAFSLQAAI' 530	VVGCNFAAVMI 540	LVFPAIL 550
h <i>Ptch-</i> 2	560 SLDLRRRHCQRLE ******	****	****	*** . ****	* * * * * * *
mPatched2	SLDLRRRHRQRLI 560	OVLCCFSSPCS 570	AQVIQMLPQE 580	LGDRAVPVGI. 590	AHLTATV 600
h <i>Ptch-</i> 2	610 QAFTHCEASSQH <sup>V</sup> *******	*****	*.****	** * * * * * * * *	***.**
mPatched2	OAFTHCEASSQH'	VVTILPPQAHL 620	LSPASDPLGS	ELYSPGGSTR	DLLSQEE 650
hPtch-2	660 ETRQKAACKSLP * ****	670 CARWNLAHFAF **.* *****	680 RYQFAPLLLQS	690 · SHAKAIVLVLF . * * * . * * *	700 GALLGLS ****
mPatched2	GTGPQAACRPLL 660	CAHWTLAHFAF 670	RYQFAPLLLQT 680	RAKALVLLFF 690	GALLGLS 700

FIG. 8B

h <i>Pich-</i> 2 mPatched2	710 LYGATLVQDGLAL ******** LYGATLVQDGLAL 710	****	****	*****	****
	760	770	780	790	800
hPtch-2	HSQRALFDLHQRE	'SSLKAVLPPPA ********	\TQAPRTWLH\ :*****	YYRNWLQGIQ <i>F</i> *** ******	AFDQDW *****
mPatched2	HSQRALFDLHQRE				
	760	770	780	790	800
	810	820	830	840	850
h <i>Ptch-</i> 2	ASGRITRHSYRNO	SEDGALAYKLI	JIQTGDAQEPI	LDFSQLTTRKI	LVDREGL
nPicn-2	****	****	****	****	***.**
mPatched2	ASGRITCHSYRNO			LDFSQLTTRKI 840	LVDKEGL 850
	. 810	820	830	840	830
	860	870	880	890	, 900
h <i>Ptch</i> -2	IPPELFYMGLTV	WSSDPLGLAAS	SQANFYPPPP	EMLHDKYDTT(	GENLRIP
	****	****	****	* * * * * * * * * * * *	* * * * * * * ~ DNI D T D
mPatched2	IPPELFYMGLTV 860	WVSSDPLGLAAS 870	880	890	900
	910	920	930	940	950
h <i>Ptch</i> -2	PAOPLEFAOFPF	LLRGLOKTADF'	VEAIEGARAA	CAEAGQAGVH	AYPSGSP
	******	** ******	* * * * * * * * *	* - * * * * * * * *	* * * * * *
mPatched2	AAQPLEFAQFPF		VEAIEGARAA 930	CTEAGQAGVH. 940	AYPSGSP 950
	910	920	9.30	940	230
	960	970	980	990	1000
h <i>Ptch-</i> 2	FLFWEQYLGLRR	CFLLAVCILLV	CTFLVCALLL	LNPWTAGLIV	LVLAMMT
	****	****	*****	* * * * * * * * *	*****
mPatched2	FLFWEQYLGLRR	970	980	990	1000
	960	270	200		
	1010	1020	1030	1040	1050
h <i>Ptch-</i> 2	VELFGIMGFLGÍ *******	KLSAIPVVILV	ASVGIGVEFT	VHVALGFLTT	QGSRNLR
mPatched2	**************************************	KI.GATPVVTI.V	ASTGIGVEFT	'VHVALGFLT'S	HGSRNLR
mraccheuz	1010	1020	1.030	1040	1050

FIG. 8C

	1060	1070	1080	1090	1100
h <i>Ptch-</i> 2	AAHALEHTFAPVT	DGAISTLLGL	LMLAGSHFDF	IVRYFFAALT	/LTLLGL
14 1011 =	** *** ****	***.****	*****	* * * * * * * * * *	****
mPatched2	AASALEQTFAPVT	DGAVSTLLGL	LMLAGSNFDF	IIRYFFVVLT	VLTLLGL
	1060	1070	1080	1090	1100
	1110	1120	1130	1140	1150
10.10	LHGLVLLPVLLSI	LGPPPEVIQM	YKESPEILSP	PAPQGGGLRW(	GASSSLP
hPtch-2	**** *****	*****.*.*.	*****. *	. * * * * * * * *	* *
mPatched2	LHGLLLLPVLLSI	LGPPPQVVQV	YKESPQTLNS	AAPQRGGLRW:	DRPPTLP
mz acoco.	1110	1120	1130	1140	1150
,	1160	1170	1180	1190	1200
t n. t o	QSFARVTTSMTVA	IHPPPLPGAY	THPAPDEPPW	ISPAATSSGNL	SSRGPGP
h <i>Ptch-</i> 2	****	. * * * * * * * *	. * * * * *		
mPatched2	QSFARVTTSMTVA				
mr accineda	1160	1170	1180		
h <i>Ptch</i> -2	ATG				

FIG. 8D

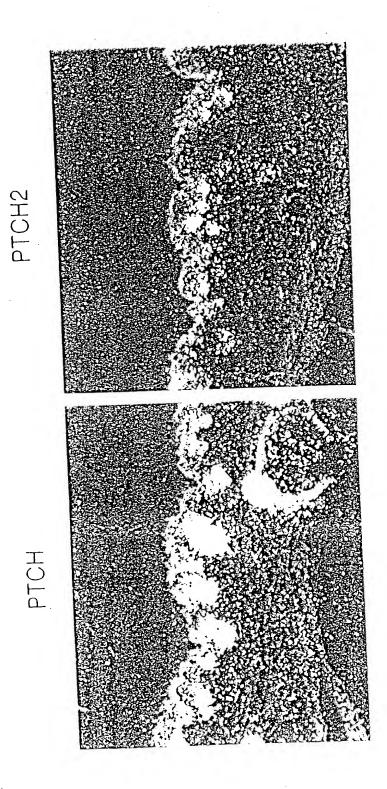


FIG. 9

consensus Sequence-of human patched 2 cDNA-clon tensch: 4004 bp 2

# d (8:01 to 10:8)

respendict acquerater creecerece erecreere remenaga erereseem 1 CCCACGCGTC CGGGAGAAGC TGGGGGAGGA GGCTGCATAC ACCTCTCAGA TGCTGATACA GACCGCACGC CAGGAGGGAG AGAACATCCT CACACCGGAA GGGTGCGCAG GCCCTCTTCG ACCCCCTCCT CCGACGTATG 101 GCACTTGGCC TCCACCTCCA GGCAGCCCTC ACTGCCAGTA AAGTCCAAGT ATCACTCTAT GGGAAGTCCT GGGATTTGAA CAAAATCTGC TACAAGTCAG CGTGAACCGG AGGIGGAGGI CCGTCGGGAG IGACGGICAI TICAGGTICA TAGIGAGAIA CCCTICAGGA CCCTAAACTI GTITTAGACG

201 GAGTICCCCT TATIGAAAAT GGAATGATIG AGCGGATGAT TGAGAAGCTG TTTCCGTGCG TGATCCTCAC CCCCCTCGAC TGCTTCTGGG AGGGAGCCAA CTCAAGGGGA ATAACTITIA CCTTACTAAC TCGCCTACTA ACTCTTCGAC AAAGGCACGC ACTAGGAGTG GGGGGAGCTG ACGAAGACCC TCCCTCGGTT

ACTECAAGGG GGETECGGET ACCTGECGGET ECCAATGTGG ETEAEGAGET GAGTGGGGGE TGECATGGET TETECECACAA ATTEATGEAE TGGEAGGAGG TGAGGITCCC CCGAGGCGGA TGGACGGCGA GGGITACACC GA&TGCTCGA CTCACCCCCG ACGGIACCGA AGAGGGIGIT TAAGTACGIG ACCGICCTCC 301

401 ANTIGCTECT GGGAGGCATG GCCAGAGACC CCCAAGGAGA GCTGCTGAGG GCAGAGGCCC TGCAGAGCAC CTTCTTGCTG ATGAGTCCCC GCCAGCTGTA TTAACGACGA CCCTCCGTAC CGGTCTCTGG GGGTTCCTCT CGACGACTCC CGTCTCCGGG ACGTCTCGTG GAAGAACGAC TACTCAGGGG CGGTCGACAT

501 CGAGCATTIC CGGGGTGACT ATCAGACACA TGACATIGGC TGGAGTGAGG AGCAGGCCAG CACAGTGCTA CAAGCCTGGC AGCGGCGCTT IGTGCAGGTC GCTCGTAAAG GCCCCACTGA TAGICTGTGT ACTGTAACCG ACCTCACTCC TCGTCCGGTC GTGTCACGAT GTTCGGACCG TCGCCGCGAA ACACGTCCAG

601 GGTATGGACA AGGACAGGGG GGTGCCCTGA GGCCATTCCC TCCTCCTGCC CCCTCCTATC CACCCTGTTT CTCCAGCTGG CCCAGGAGGC CCTGCCTGAG CCATACCTGT TCCTGTCCCC CCACGGGACT CCGGTAAGGG AGGAGGACGG GGGAGGATAG GTGGGACAAA GAGGTCGACC GGGTCCTCCG GGACGGACTC

TTGCGAAGGG TCGTCTAGGT ACGSAAGAGG AGGTGGTGGG ACCTACTGTA GGACGTACGC AAGAGACTTC AGTCACGACG GGCACACCAC CCTCCGATAG AACGCITICCO AGCAGATICOA TGCCITICTOO TCCACCACOO TGGATGACAT CCTGCATGOG ITCTCTGAAG TCAGTGCTGC CCGTGTGGTG GGAGGCTATO 701

TECTCATEGT BESTETTECA CETEGERACET TECCECEREC CERCETECRA CERGTECECA CECTGGGGAG CECETGAGAE TECCETTTEC CECCACAGET ACGAGTACCA CCCAGAACGT GGACCGTGGA ACGGGGGTGG GGTGGAGGTT GGTCACGGGT GGGACCCCTC GGGGACTCTG ACGGGAAAGG GGGGTGTCGA 801

# FIG. 10A

901 GOCCTATGCC TGTGTGACCA TGCTGCGGTG GGACTGCGCC CAGTCCCAGG GTTCCGTGGG CCTTGCCGGG GTACTGCTG TGGCCCTGGC GGTGGCCTCA CCGGATACGG ACACACTGGT ACGACGCCAC CCTGACGCGG GTCAGGGTCC CAAGGCACCC GGAACGGCCC CATGACGACC ACCGGGACCG CCACCGGAGT

AGACACGGGA CGAGCCGTAG TGGAAGTTAC GACGGTGATG GGTCCATGCG GTCCTGACGT CCCGTCTGAG TCACGGTCAG TGGTCCGAAG GGGCAGACTC AGTGCCAGTC ACCAGGCTTC GCTCGGCATC ACCITCAATG CTGCCACTAC CCAGGTACGC CAGGACTGCA GOCTTGGGC TCTGTGCCCT 1001

TGCCCAGGAG TCGACGGGG AGGAGGGGG GAGGTCCACG ACGGGAAGAA CTGAGACCCT TAGCCGCACC TACTGCATAA GGACGACCGC GTACGGAAGT CATGCCTTCA AGETGCCCGC TCCTCTGCCC CTCCAGGTGC TGCCCTTCTT GACTCTGGGA ATCGGCGTGG ATGACGTATT CCTGCTGGCG CCGGAACCCG 1101 ACGGGTCCTC

CAGAGGCTCT GCCTGGCACC CCTCTCCAGG TGGGGCCTTG TCCCCCAGGG CTCATCTGAG GCAGCTCAGC TTACTGGTTA AGAGCCTCTT GGTTCAAGTG

ACCTIGGGCT GCTAATGAAC CTCGGTGCCT CTTGTCCCCA TGTGTAAACA GGGAAATAA TAGTGCTGTG TCCTAAGGGT TATTGTTTGG ATCAGTGAAG GTCTCCGAGA CEGACCGTGG GGAGAGGTCC ACCCCGGAAC AGGGGGTCCC GAGTAGACTC CGTCGAGTCG AATGACCAAT TCTCGGAGAA CCAAGTTCAC 1201

TGGAACCCGA CGATTACTTG GAGCCACGGA GAACAGGGGT ACACATTTGT CCCCTTTATT ATCACGACAC AGGATTCCCA ATAACAAACC TAGTCACTTC 1301

ATTGAGTICA ACTIACGAAT CIIGICGGGT AGTATGCAIG TACCAIGGGI TATTTACGAI CGGIGACACA ATACTGACGG GGIGGAGACG IGGGGITCAA TAACTCAAGT TGAATGCTTA GAACAGCCCA TCATACGTAC ATGGTACCCA ATAAATGCTA GCCACTGTGT TATGACTGCC CCACCTCTGC ACCCCAAGTT 1401

CACTITGACA CGGCCCTCC CITGIGACCI GAGGCAGGI CCCCACTCTG ICCTGGCAGG AGCGCAIGGG CGAGIGICTG GGACTCGGAG GGGAAGTGAG GTGAAACTGT GCCGGGGAGG GAACACTGGA CTCCCGTCCA GGGGTGAGAC AGGACCGTCC TCGCGTACCC GCTCACAGAC CCTGAGCCTC 1501

CAGGGCACGG GCACCAGTGT TGTACTCACA TCCATCACA ACATGGCCGC CTTCCTCATG GCTGCCCTCG TTCCCATCCC TGCGCTGCGA GCCTTCTCCC STOGOGIGOO CGIGGICACA ACAIGAGIGI AGGIAGIIGI IGIACCGGOG GAAGGAGIAC CGACGGGAGO AAGGGIAGGG ACGOGACGOI CGGAAGAGGG 1601

TACAGCCTGG ACCTACGGCG GCGCCACTGC CAGCGCCTTG ATGTGCTCTG CTGCTTCTCC AGGTACTGCC TGCGCCCCAG CCCCTTCCTC CCGTGACCCA TEGATECCEC CECEGTGACE GTCECEGAAC TACACGAGAC GACGAAGAGG TCCATGACGG ACGCGGGGTC GGGGAAGGAG GGCACTGGGT ATGTCGGACC 1701

CECCABECTE TECESTEACE AGEATTEAA GGEACAGACE TETEATECAE TETETACETE TECEAGTECE TGCTCTGCTC AGGTGATTCA GATECTGEEC 1801

1901 CAGGAGCTGG GGGACGGGAC AGTACCAGTG GGCATTGCCC ACCTCACTGC CACAGTTCAA GCCTTTACCC ACTGTGAAGC CAGCAGCCAG CATGTGGTCA GICCICGACC CCCIGCCCIG ICAIGGICAC CCGIAACGGG IGGAGIGACG GIGICAAGIT CGGAAAIGGG IGACACITCG GICGICGGIC GIACACCAGI

2001 CCATCCTGCC TCCCCAAGCC CACCTGGTGC CCCCACCTTC TGACCCACTG GGCTCTGAGC TCTTCAGCCC TGGAGGGTCC ACACGGGACC TTCTAGGCCA GETAGACCE AGGGTTCGG GTGGACCACE GGGGTGGAAG ACTGGGTGAC CCGAGACTCG AGAAGTCGGG ACCTCCCAGG TGTGCCCTGG AAGATCCGGT

GGAGGAGGAG ACAAGGCAGA AGGCAGCCTG CAAGTCCCTG CCCTGTGCCC GCTGGAATCT TGCCCATTTC GCCCGCTATC AGTTTGCCCC GTTGCTGCTC COTOCTOCTO TGITCCGTOT TOOGTOGGAO GITCAGGGAO GGGACACGGG CGACOTTAGA ACGGGTAAAG CGGGCGATAG TCAAACGGGG CAACGACGAG 2101

GCCCTGACGG GTCAGTGTAC GSTICCGGTA GCACGACCAC GAGAACCAC GAGAAGACCC GGACTCGGAG AIGCCTCGGT GGAACCACGI TCTGCCGGAC CGGGACTGCC 2201 CAGTCACATG CCAAGGCCAT GGTGCTGGTG CTCTTTGGTG CTCTTCTGGG CCTGAGCCTC TACGGAGCCA CCTTGGTGCA AGACGGCCTG

TACACCACGG AGCCCCGTGG TTCCTCGTAC GGAAGGACTC GCGGGTCGAG TCCATGAAGA GGGACATGCT CCACCGGGAC CACTGGGTCC CACCGAAACT AIGIGGIGCC TOGGGGCCACC AAGGAGCATG CCTTCCTGAG CGCCCAGCTC AGGTACTTCT CCCTGTACGA GGTGGCCCTG GTGACCCAGG GTGGCTTTGA 2301

2401 CTACGCCCAC TCCCAACGCG CCCTCTTTGA TCTGCACCAG CGCTTCAGTT CCCTCAAGGC GGTGCTGCCC CCACGGCCA CCCAGGCACC CCGCACCTGG GATECCEGTE AGGETTGCGC GGAGAAACT AGACGTGGTC GCGAAGTCAA GGGAGTTCCG CCACGACGGG GGTGGCCGGT GGGTCCGTGG GGCGTGGACC

GACGTGATAA TGGCGTTGAC CGATGTCCCT TAGGTCCGAC GGAAACTGGT CCTGACCCGA AGACCCGCGT AGTGGGCGGT GAGCATGGCG TTACCGAGAC 2501 CTGCACTATT ACCGCAACTG GCTACAGGGA ATCCAGGCTG CCTTTGACCA GGACTGGGCT TCTGGGCGCA TCACCCGCCA CTCGTACCGC AATGGCTCTG

TCCTACCCCG GGACCGGATG TTCGACGAGT AGGTCTGACC TCTGCGGGTC CTCGGAGACC TAAAGTCGGT CCAACCCTCT CCCGACCTCC CCAGGTGATC 2601 AGGATGGGGC CCTGGCCTAC AAGCTGCTCA TCCAGACTGG AGACGCCCAG GAGCCTCTGG ATTTCAGCCA GGTTGGGAGA GGGCTGGAGG GGTCCACTAG

TACAGGGGCT GCAGGCCTCC TGGGCCCAGG CCTTCAGCCC TCTCTGCCTC TGCAGCTGAC CACAAGGAAG CTGGTGGACA GAGAGGGACT GATTCCACCC ATGTCCCCGA CGTCCGGAGG ACCCGGGTCC GGAAGTCGGG AGAGACGGAG ACGTCGACTG GTGTTCCTTC GACCACCTGT CTCTCCTGA CTAAGGTGGG 2701

CTCGAGAAGA TGTACCCCGA CTGGCACACC CACTCGTCAC TGGGGGACCC AGACCGTCGG AGTGTCCGGT TGAAGATGGG GGGTGGAGGA CTTACCGACG 2801 GAGCTCTTCT ACATGGGGCT GACCGTGTG GTGAGCAGTG ACCCCCTGGG TCTGGCAGCC TCACAGGCCA ACTTCTACCC CCCACCTCCT GAATGGCTGC

2901 ACGACAANTA CGACACCACG GGGGAGAACC TICGCAGTGA GTCTIGGGGG GAGCTCGGCA AGAGCCTCAG CCTCGCCCAC ACAAGCCCTG AGCCTGAGGC rectetthat scretegese eceptates aascsteact eagaaceee ctegageest teteggaste sgagegggis tsticggae teggaetees

3001 CCIGCCCACT CIGCCCCGIG CICACCGCCC IGICCCTCIC CCTCTTCICC CTTCCCCTCC CCTCCACAGT CCCGCCAGCT CAGCCCTIGG AGITIGCCCA GGACGGETGA GACGGGGCAC GAGTGGCGGG ACAGGGAGAG GGAGAAGAGG GAAGGGGAGG GGAGGTGTCA GGGCGGTCGA GTCGGGAACC TCAAACGGGT

# FIG. 10C

GACTGCAGAC TITGIGGAGG CCAICGAGGG GGCCCGGGCA GCAIGCGCAG AGGCCGGCCA GGCIGGGGIG CCGACCCCAC CAAGGGGAAG GACGACGCAC CGGAGGTCTT CTGACGTCTG AAACACCTCC GGTAGCTCCC CCGGGCCCGT CGTACGCGTC TCCGGCCGGT 3101 GITCCCCITC CIGCIGCGIG GCCTCCAGAA

GTGCGGATGG GGTCGCCGAG GGGGAAGGAG AAGACCCTTG TCATAGACCC GGACGCCGCG ACGAAGGACG ACCGGCAGAC GTAGGACGAC CACACGTGAA CATCCTGCTG TGGCCGTCTG CACGCCTACC CCAGCGGCTC CCCCTTCCTC TTCTGGGAAC AGTATCTGGG CCTGCGGGGG TGCTTCCTGC 3201

recresters recretects erecreaace ecresacese resecteara stsassectr seassasses ssacasasae acceaect recersecea AGGAGCAGAC ACGAGACGAC GAGGAGTTGG GGACCTGCCG ACCGGAGTAT CACTCACGAA CGTCCTCACC CCTGTCTCTG TGGGGTGGGA AGGGACGGGT 3301

CGGACAGTAG GGAGGACGGT CCTCGGGAGA CACTCGGGAC AGAGGGAGTC CACGACCAGG ACCGCTACTA CTGTCACCTT GAGAAACCAT AGTACCCAAA GRACCCTCT GTGAGCCCTG TCTCCCTCAG GTGCTGGTCC TGGCGATGAT GACAGTGGAA CTCTTTGGTA TCATGGGTTT CCTCCTGCCA GCCTGTCATC 3401

CCTGGGCAIC AAGCTGAGTG CCATCCCCGT GGTGATCCTT GTGGCCTCTG TAGGCATTGG CGTTGAGTTC ACAGTCCACG TGGCTCTGGT GAGCACGGGC SGACCCGTAG TICGACTCAC GGTAGGGGCA CCACTAGGAA CACCGGAGAC ATCCGTAACC GCAACTCAAG TGTCAGGTGC ACCGAGACCA CTCGTGCCCG 3501

ACCCCGGGGA GGGACCAATC AGCTGATTCA GTATTCAACA CATATTGTTC AAGCCCCTAC TATGTGCTAG GTACTAITTA AGAATTTGGG CTGGGTGGAC CCTGGTTAG TCGACTAAGT CATAAGTTGT GTATAACAAG TTCGGGGATG ATACACGATC CATGATAAAT TCTTAAACCC GACCCACCTG TGGGGCCCCT 3601

GIGGIGGCIC ATTCCIGIAA TCCCAGCACT TIGGGAGGCC GAGGCGGGIG GATCACCTGA GGICGGGAGI TCGAAACCAG CCIGGCCAAC AIGGIGAAAC CACCACCGAG TAAGGACATT AGGGTCGTGA AACCCTCCGG CTCCGCCCAC CTAGTGGACT CCAGCCCTCA AGCTTTGGTC GGACCGGTTG TACCACTTTG 3701

3801 CCTGTCTTTA CTAAAAATAC AAAAATTAG CCAGGCGTGG TGGCACATGC CAGTAGTCCC AGCTACTTTG GAGGCTGAGG CAGAATTGCT TGAACCTGGG GGACAGAAAT GATTITTATG TITTITAATC GGTCCGCACC ACCGTGTACG GTCATCAGGG TCGATGAAAC CTCCGACTCC GTCTTAACGA ACTTGGACCC

ICCGCTICCA ACGICACTICG ACTITAGCAC GGIAACGIGA GGICGGACCC GIIGIICICA CGIIGAGAGG CAGAGIIIII IIIIIIIII 3901

4001 GCGA

**₹** 

CGCT

FIG. 10D

# AAGGCCGTAC TGAGCTAGCG GCGGGAGTC TCTCGACGGG GGCTCAATGT GTGGGGTCG AGCTTGGCGT CGTGGGGGTCT AGGATCGACC CTCGGACTTC GCTCTTTCTG GGACTGTTGG

CGAGGIGAGA CCGAAGCACG AAIGAAGGIC CCGGACGAGA AGAGAGACCC TACGCCCIAG GICICIGIAA CACCGIIIICA CGAGAAAGAC CCIGACAACC 101 GETCCACTET GGETTEGTGE TACTTECAG GGECTGETET TETETETGGG ATGEGGGATE CAGAGACATT GTGGCAAAGT

TTCGGGATG ACTCGATCGC CGCCCCTCAG AGAGCTGCCC CCGAGTTACA CACCCCCAGC TCGAACCGCA GCACCCCAGA TCCTAGCTGG GAGCCTGAAG

CONTIGGGGC CONGCOATTA GETOTOGGCA TGGCCATTAT TGAGACAAC TTGGAACAGC TOTGGGTAGA AGTGGGCAGO CGGGTGAGCO AGGAGCTGCA GGAAACCCCG GGACCGIAAI CCAGAGGCGI ACCGGIAAIA ACTCIGITTG AACCTTGTCG AGACCCATCT TCACCCGICG GCCCACTCGG ICCTCGACGI 201

TTACACCAAG GAGAAGCTGG GGAGGAGGC TGCATACACC TCTCAGATGC TGATACAGAC CGCACGCCAG GAGGGAGAGA ACATCCTCAC ACCCGAAGCA CTCCCTCTCT TGTAGGAGTG TGGGCTTCGT AATGTGGTTC CTCTTCGACC CCCTCCTCCG ACGTATGTGG AGAGTCTACG ACTATGTCTG GCGTGCGGTC 301

CTTGGCCTCC ACCTCCAGGC AGCCCTCACT GCCAGTAAG TCCAAGTATC ACTCTATGGG AAGTCCTGGG ATTTGAACAA AATCTGCTAC AAGTCAGGAG GAACCGGAGG TGGAGGTCCG TCGGGAGTGA CGGTCATTTC AGGTTCATAG TGAGATACCC TTCAGGACCC TAAACTTGTT TTAGACGATG TTCAGTCCTC 401

AAGGGGAATA ACTITIACCI TACTAACTCA CCTACTAACT CTICGACANA GGCACGCACT AGGAGTGGGG GGAGCTGACG AAGACCCTCC CTCGGITTGA TICCCCTIAI IGAAAAIGGA AIGATIGAGI GGAIGAITGA GAAGCIGITI CCGIGCGIGA ICCICACCCC CCICGACTGC TICIGGGAGG GAGCCAAACT 501

CCAAGGGGGC TCCGCCTACC TGCCCGGCCG CCCGGATATC CAGTGGACCA ACCTGGATCC AGAGCAGCTG CTGGAGGAGC TGGGTCCCTT TGCCTCCTTT GGTTCCCCCG AGGCGGATGG ACGGGCCGGC GGGCCTATAG GTCACCTGGT TGGACCTAGG TCTCGTCGAC GACCTCCTCG ACCCAGGGAA ACGGAGGAAA 601

701 GAGGGCTTCC GGGGCTGCT AGACAAGGCA CAGGTGGGCC AGGCCTACGT GGGGGGCCC TGTCTGCACC CTGATGACCT CCACTGCCCA CCTAGTGCCC CTCCCGAAGG CCCTCGACGA TCTGTTCCGT GTCCACCCGG TCCGGATGCA CCCCGCCGGG ACAGACGTGG GACTACTGGA GGTGACGGGT GGATCACGG

801 CCAACCATCA CAGCAGGCAG GGTCCCAATG TGGCTCACGA GCTGAGTGGG GGCTGCCATG GCTTCTCCCA CAAATTCATG CACTGGCAGG AGGAATTGCT GGTTGGTAGT GTCGTCCGTC CGAGGGTTAC ACCGAGTGCT CGACTCACCC CCGACGGTAC CGAAGAGGGT GTTTAAGTAC GTGACCGTCC TCCTTAACGA

GETEGGAGGE ATGGECAGAG ACCECEAAGG AGAGETGETG AGGGEAGAGG ECETGEAGAG CACETTETTG ETGATGAGTE ECEGECAGET GTACGAGEAT CGACCCTCCG TACCGGTCTC TGGGGGTTCC TCTCGACGAC TCCCGTCTCC GGGACGTCTC GTGGAAGAAC GACTACTCAG GGGCGGTCGA CATGCTCGTA 901

# FIG. 11A

TGTGGTCACC

AAGGCCCCAC TGATAGICIG IGTACIGIAA CCGACCICAC ICCICGICCG GICGIGICAC GAIGITCGGA CCGICGCCGC GAAACACGIC GACCGGGTCC GGCTGGAGTG AGGAGCAGGC CAGCACAGTG CTACAAGCCT GGCAGCGGCG CTTTGTGCAG CTGGCCCAGG 1001 TTCCGGGGTG ACTATCAGAC ACATGACATT

AGGCCCTGCC TGAGAACGCT TCCCAGCAGA TCCATGCCTT CTCCTCCACC ACCTTGGATA ACATCCTGCA TGCGTTCTCT GAAGTCAGTG CTGCCCGTGT TECGGGACGG ACTETTGEGA AGGGTEGTET AGGTAEGGAA GAGGAGGTGG TGGGAECTAT TGTAGGAEGT AEGEAAGAGA ETTEAGTEAE GAEGGGEACA 1101

1201 GGIGGGAGGC TATCIGCTCA IGCIGGCCIA IGCCIGIGIA ACCAIGCIGC GGIGGGACTG CGCCCAGICÇ CAGGGITCCG IGGGCCTIGC CGGGGTACIG CCACCCTCCG ATAGACGAGT ACGACCGGAT ACGGACACAC TGGTACGACG CCACCCTGAC GCGGGTCAGĠ GTCCCAAGGC ACCCGGAACG GCCCCATGAC

GACCACCGGG ACCGCCACCG GAGTCCGGAA CCCGAGACAC GGGACGAGCC GTAGTGGAAG TTACGACGGT GATGGGTCCA CGACGGGAAG AACCGAGACC CICAGGCCTT GGGCTCTGTG CCCTGCTCGG CATCACCTTC AATGCTGCCA CTACCCAGGT GCTGCCCTTC TTGGCTCTGG TGGCGGTGGC CTGGTGGCCC 1301

CITAGECECA CCIACTECAT AAGGACGACE GCGTACGGAA GTGTCTCCGA GACGGACCGT GGGGAGAGGT CCTCGCGTAC CCGCTCACAG ACGTCGCGTG GAATCGGCGT GGATGACGTA TTCCTGCTGG CGCATGCCTT CACAGAGGCT CTGCCTGGCA CCCCTCTCCA GGAGCGCATG GGCGAGTGTC TGCAGCGCAC 1401

CTTACAGCCA CCCGTGGTCA CAGCATGAGT GTAGGTAGTT GTTGTACCGG CGGAAGGAGT ACCGACGGGA GCAAGGGTAG GGACGCGACG CTCGGAAGAG GAATGTCGGT GGGCACCAGT GTCGTACTCA CATCCATCAA CAACATGGCC GCCTTCCTCA TGGCTGCCCT CGTTCCCATC CCTGCGCTGC GAGCCTTCTC 1501

TOCTCAGECT GGACCTACGG CGGCGCCACT GCCAGCGCCT TGATGTGCTC TGCTGCTTCT CCAGTCCCTG CTCTGCTCAG GTGATTCAGA TCCTGCCCCA AGGAGTOGGA CCTGGATGCC GCCGCGGTGA CGGTCGCGGA ACTACACGAG ACGACGAAGA GGTCAGGGAC GAGACGAGTC CACTAAGTCT AGGACGGGGT 1601

cetebacece etsecetste atseteacee staacsssts sastsaest steaasttes saatsssts acaettesst estesstest acaeeass GACGGGACAG TACCAGTGGG CATTGCCCAC CTCACTGCCA CAGTTCAAGC CTTTACCCAC TGTGAAGCCA GCAGCCAGCA GGAGCTGGGG 1701

ATCTGCCTC CCCAAGCCCA CCTGGTGCCC CCACCTTCTG ACCCACTGGG CTCTGAGCTC TTCAGCCCTG GAGGGTCCAC ACGGGACCTT CTAGGCCAGG TAGGACGGAG GGGTTCGGGT GGACCACGGG GGTGGAAGAC TGGGTGÁCCC GAGACTCGAG AAGTCGGGAC CTCCCAGGTG TGCCCTGGAA GATCCGGTCC 1801

1901 AGGAGGAGAC AAGGCAGAAG GCAGCCTGCA AGTCCCTGCC CTGTGCCCGC TGGAATCTTG CCCATTTCGC CCCGGAATTC CTGCAGCCCG GGGGATCCAC TICCGICITC CGICGGACGI ICAGGGACGG GACACGGGCG ACCITAGAAC GGGTAAAGCG GGGCCTIAAG GACGICGGGC CCCTAGGIG

TAGTICTAGA GCGGCCGCCA CCGCGGTGGA GCTCCAGCTT TTGTTCCCTT TAGTGAGGGT TAATTGCGCG CTTGGGTATC TT ATCAAGATCT CGCCGGCGGT GGCGCCACCT CGAGGTCGAA AACAAGGGAA ATCACTCCCA ATTAACGCGC GAACCCATAG AA TAGTICTAGA GCGGCCGCCA CCGCGGTGGA GCTCCAGCTI TIGTICCCTT TAGTGAGGGT TAATTGCGCG CTTGGGTATC 2001

# FIG. 11B

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